Inorganic Arsenic
Oral Slope Factor

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DSD History

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To be determined	DSD posted as final

Executive Summary

Background

An independent quantitative carcinogenicity assessment of oral exposure to inorganic arsenic (iAs) has recently been completed by Gradient® under TCEQ work orders (No. 582-15-51942-01, 582-15-51942-05). This independent analysis focused on determining the most appropriate cancer endpoints, studies, and models to support an oral carcinogenicity assessment of iAs, and considered factors that affect the apparent potency of iAs across geographically and culturally distinct populations. Bladder and lung cancer were identified as the cancer endpoints of primary interest for iAs dose-response analyses. While the mode of action evidence support there being a threshold, making a robust quantitative demonstration of a threshold using epidemiological data is difficult. Consequently, a no threshold relationship between iAs and cancer risk was assumed in deriving toxicity factors. Meta-regression was used to pool data across studies from different regions of the world to derive oral cancer slope factors (CSFs) for iAs based on the background risks (i.e., incidences) of bladder and lung cancer in the US. The CSFs derived represent more objective measures of incremental cancer risk from iAs exposure than those previously derived using a single dataset (e.g., the Southwest Taiwanese cohort utilized in USEPA 2010). Sensitivity analyses were also conducted to determine the effect of various assumptions on the analysis (e.g., average iAs drinking water concentration versus cumulative exposure or daily iAs intake as the exposure metric, study population/location), including study quality considerations. Populations with relatively high iAs exposures appeared to drive the pooled cancer risk estimates. Additional details pertaining to the dose-response analyses for carcinogenesis due to oral exposure to iAs may be found in the scientific publication (Lynch et al. 2017). Overall, results of the meta-regression analyses show that the incremental risks of bladder and lung cancer associated with iAs are relatively low.

Oral CSF

The TCEQ will adopt an oral CSF for iAs based on the reported results (Lynch et al. 2017). The meta-regression approach with iAs concentration adjusted for water consumption and body weight (as the exposure metric) was considered to be the most robust analysis since:

1) The meta-regression approach took into account within-study correlation of the data points;
2) The number of studies using average iAs concentration was more than 2-times higher than that of studies using cumulative iAs exposure or daily iAs intake;
3) Exposures that were not adjusted for water consumption level and body weight slightly overestimated the slope; and
4) Importantly, this analysis represents a more data-informed and objective measure of incremental cancer risk from iAs exposure compared to relying on (i.e., despite multiple

study datasets, assigning 100% weight to) only a single dataset or an aggregated assessment that fails to account for differing iAs intake (e.g., water consumption, body weight) across studies.

Thus, results based on this meta-regression approach were used by the TCEQ to derive an oral CSF applicable to the US population.

The ten epidemiology studies ultimately utilized to assess iAs-induced *bladder cancer* in the preferred meta-regression analysis resulted in a slope (pooled β) of 0.0011 (p value=0.008) and an oral CSF of 7.7E-03 per mg/kg-day (95% CI of 2.0E-03, 1.3E-02) applicable to the US population. The nine studies utilized to assess *lung cancer* due to oral iAs exposure in the preferred meta-regression analysis resulted in a similar slope (pooled β) of 0.0012 (p value=0.005) and an oral CSF of 2.5E-02 per mg/kg-day (95% CI of 7.3E-03, 4.2E-02). ***Summing the CSFs for bladder and lung cancer based on these human data results in an oral CSF of 3.27E-02 per mg/kg-day. According, the TCEQ will use a CSF of 3.3E-02 per mg/kg-day to assess the carcinogenicity of chronic (e.g., lifetime) oral exposure to iAs.***

Implications

Considering these oral CSFs in conjunction with typical exposure levels in the US and Texas results in estimates of excess risk that are much lower than the underlying observed incidences of bladder and lung cancer, which supports the plausibility of the CSF estimates. Furthermore, it indicates that existing widespread exposures of the general US population to relatively low doses of iAs are unlikely to result in substantial excess cancer risks, but rather result in potential risks well within the USEPA acceptable excess risk range (1E-06 to 1E-04). For example, based on an approximate US drinking water average of 0.002 mg/L (ATSDR 2007), the estimated excess risk would be around 2E-06 (i.e., 0.002 mg/L × 2.5 L/day × 1/80 kg = 6.25E-05 mg/kg-day × 3.3E-02 per mg/kg-day = excess risk of 2.1E-06). Similarly, excess risk at the federal maximum contaminant level (MCL of 0.010 mg/L) would be 1E-05 (i.e., 0.010 mg/L × 2.5 L/day × 1/80 kg = 3.13E-04 mg/kg-day × 3.3E-02 per mg/kg-day = excess risk of 1.0E-05). Finally, based on a US dietary iAs mean intake range of perhaps 0.0032-0.0102 mg/day with intakes as high as 0.020-0.105 mg/day (ATSDR 2007), the associated estimated excess risks would be around 2E-06 to 5E-06 for mean intake (e.g., 0.0032 mg/day × 1/70 kg = 4.57E-05 mg/kg-day × 3.3E-02 per mg/kg-day = excess risk of 1.5E-06) and approximately 1E-05 to 5E-05 at the highest end of estimated intakes (e.g., 0.020 mg/day × 1/70 kg = 2.86E-04 mg/kg-day × 3.3E-02 per mg/kg-day = excess risk of 9.4E-06).

Regarding implications for surface soil, it is noted that substituting the oral CSF (3.3E-02 per mg/kg-day) based on the recent multiple study, meta-regression dose-response analyses (Lynch et al. 2017) for the USEPA CSF from the 1980's (1.5 per mg/kg-day) based solely on a Taiwanese

subpopulation (USEPA 1988) in the USEPA Regional Screening Level preliminary remediation goal (PRG) calculator (https://epa-prgs.ornl.gov/cgi-bin/chemicals/csl_search) results in a residential surface soil PRG of 29.8 ppm at a target 1 in 1,000,000 excess risk level. This PRG is above typical central tendency background levels (e.g., in Smith et al. 2013, the US Geological Survey reports median and mean surface soil (0-5 cm) arsenic concentrations of 5.2 and 6.4 ppm, respectively). The residential surface soil PRG at a target 1 in 100,000 excess risk level would be 298 ppm, which is above the range of typical arsenic background concentrations (e.g., the 95th, 97.5th, and 99.9th percentiles of the US Geological Survey data referenced in Smith et al. 2013 for arsenic in surface soil (0-5 cm) are 13.1, 16.1, and 85.1 ppm, respectively). The estimated excess risk associated with a mean surface soil concentration of 6.4 ppm (Smith et al. 2013) would be around 2E-07 (i.e., 6.4 /29.8 ppm $\times$ 1E-06 = excess risk of 2.1E-07).

Summing the estimated mean excess risks for drinking water (2.1E-06), dietary intake (3.2E-06 as the midpoint of estimates), and surface soil (2.1E-07) results in a multi-media mean excess risk estimate of 5.5E-06, well within USEPA's acceptable excess risk range (1E-06 to 1E-04). Including inhalation excess risk associated with estimated statewide means of arsenic in ambient air PM_{10} (0.0020 µg/m^3 as a hypothetical lifetime average based on 2006-2015 TCEQ network data) or $PM_{2.5}$ (0.00026 µg/m^3 as a hypothetical lifetime average) would result in insignificant additional risk (e.g., 0.0020 µg/m^3 $\times$ 1.5E-04 per µg/m^3 (TCEQ 2012) = excess inhalation risk of 3.1E-07). Even summing the excess risk estimates associated with the federal MCL (1.0E-05), the highest estimated upper end of the dietary iAs intake range (5.0E-05), and the 99.9th percentile of surface soil concentrations (2.9E-06) results in a multi-media excess risk (6.3E-05) within USEPA's acceptable excess risk range. Still, it is likely that this oral CSF (3.3E-02 per mg/kg-day for the US) overestimates risk and thus represents a conservative estimate of excess risk for the US population US because:

- Some of the factors that likely increase an individual's susceptibility to iAs-induced cancer (e.g., diets low in folate, selenium, and protein) are uncommon in the US;
- Dietary intake of iAs in the US is lower relative to most populations in the iAs literature (e.g., Bangladesh and Taiwan), which also favors the overestimation of potency/risk when applied to the US population; and
- Drinking water iAs levels in the US are generally not as high as those used in these studies (on the order of 200-300 µg/L) and the likelihood of a threshold in the association between iAs and cancer is supported by the underlying epidemiological evidence, which generally show a lack of a significant relationship in US studies, particularly at drinking water iAs concentrations below approximately 100 µg/L (e.g., over 99.9% of all public drinking water samples in Texas (January 2006-June 2016) are lower, with the statewide mean being 20-fold lower at 5 µg/L).

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